



## Case report

## Death in patients with adaptive servo-ventilation for sleep apnea and no specific SERVE-HF profile: A case series study

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## ARTICLE INFO

## Keywords:

Heart failure  
Sleep apnea  
Hunter-Cheyne-Stokes breathing  
Adaptive servo-ventilation

## ABSTRACT

**Purpose:** The SERVE-HF study reported a risk of cardiovascular death associated with adaptive servo-ventilation (ASV) for central sleep apnea in patients with chronic heart failure with reduced left ventricular ejection fraction (LVEF). Therefore, we adopted in May 2015 a safety procedure in our 32 patients with ASV since 2006. It led to ASV removal in four patients due to  $\leq 45\%$  LVEF. At the end of the procedure we noted eight cases of death. This high 25% mortality rate led us to study these cases.

**Methods:** The study population was derived from our database of patient follow-up from the sleep unit of our cardiovascular department.

**Results:** All deceased patients but one had cardiac disorders but only one matched the SERVE-HF patient profile. ASV was due to predominant central ( $n = 4$ ) or mixed ( $n = 4$ ) sleep apnea. Six patients died prior to our procedure including two patients who died several months after ASV cessation, one from ventricular fibrillation and one from respiratory infection. The cases with ongoing ASV consisted in one case of end-stage heart failure with asystole, two cases of cancer and one case of suicide. Two patients died after their safety procedure with no contra-indications to ASV and before study completion in all the patients, one from cancer and one from pulmonary and renal disorders.

**Conclusions:** In this series, no relationship became apparent between sleep apnea or ASV and death. Cardiovascular deaths were not predominant. Further study will be required to clarify the risks associated with ASV in patients with cardiovascular disease.

## 1. Introduction

The SERVE-HF study reported an increased risk of cardiovascular death associated with adaptive servo-ventilation (ASV) for predominant central sleep apnea in patients with chronic heart failure (CHF) with reduced left ventricular ejection fraction (LVEF) [1]. Consequently, in May 2015 we adopted a safety procedure in the 32 patients equipped by us with ASV since 2006. At the end of the procedure we noted eight cases of death. This high 25% mortality rate led us to study these cases.

## 2. Material and methods

As a cardiovascular department with a sleep unit, uninvolved in the SERVE-HF study, we paid particular attention to the Special Safety Notice received on May 18, 2015 from the American Academy of Sleep Medicine (AASM) relating a ResMed notification launched five days

earlier concerning preliminary results of the SERVE-HF study. Within two weeks a total of 32 patients treated with ASV for sleep apnea were identified from our follow-up database of patients ventilated for sleep apnea, the first patients being equipped with ASV in 2006. Individual consultations were scheduled to explain the ventilator Safety Notice and the necessity to re-assess patients' medical files in light of the SERVE-HF study. The proposal included an echocardiogram to determine their present LVEF, previously measured or not. The initial goal of this safety procedure was to determine whether ASV could be continued in each patient with respect to the Safety Notice. All the patients could be contacted except six as they were deceased. Two others died seven weeks (Aug 2015) and 28 weeks (Jan 2016), respectively, after the re-assessment of their case and before the end of the safety procedure i.e. before the last patient could be seen and echocardiogrammed in March 2016 (Fig. 1).

In the 32 patients we collated clinical characteristics, reasons for

*Abbreviations list:* AASM, American Academy of Sleep Medicine; ASV, adaptive servo-ventilation; CHF, chronic heart failure; CPAP, continuous positive airway pressure; HCSB, Hunter-Cheyne-Stokes breathing; LVEF, left ventricular ejection fraction

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<https://doi.org/10.1016/j.rmcr.2018.11.017>

Received 16 January 2018; Received in revised form 22 November 2018; Accepted 23 November 2018

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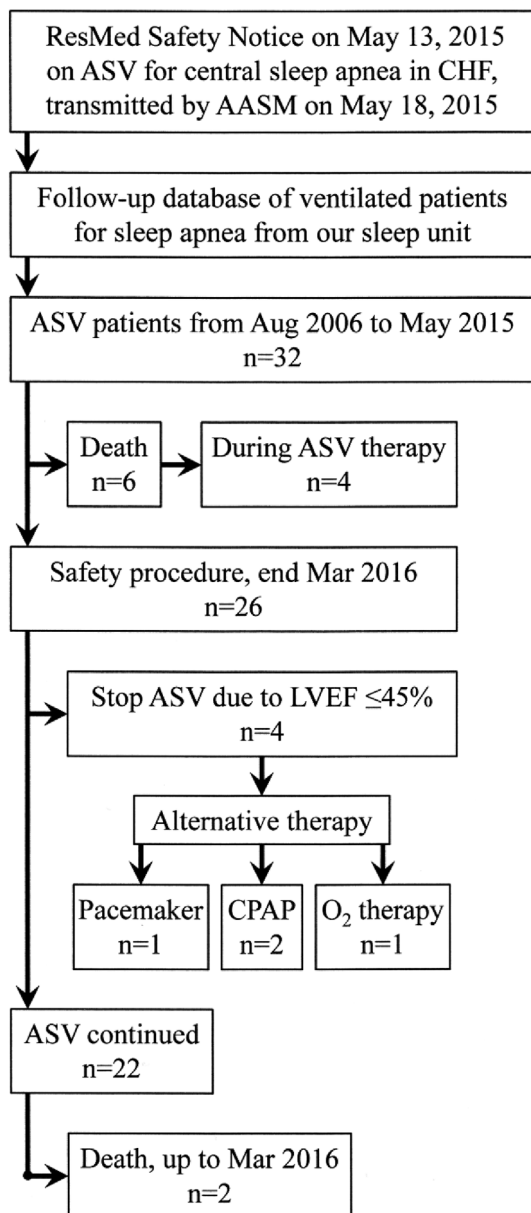


Fig. 1. Flow diagram of the study. AASM: American Academy of Sleep Medicine; ASV: adaptive servo-ventilation; CHF: chronic heart failure; CPAP: continuous positive airway pressure; LVEF: left ventricular ejection fraction.

sleep investigation, results of nocturnal polygraphy recordings and reasons for ASV. We also noted LVEF measurement at the time of our safety procedure as well as the decision to interrupt ASV or not and the alternative chosen, as the case may be. Regarding the deceased patients, all available information about the circumstances of death was also collected. The nocturnal cardiorespiratory polygraphies, all performed in our laboratory using an Embletta<sup>®</sup> PDS system (Medcare Flaga, Reykjavik, Iceland), were visually re-analyzed by two experienced sleep medicine specialists using standard criteria from the AASM-2016 guidelines [2]. Apnea was characterized obstructive, central or mixed and hypopnea obstructive or central in nature.

### 2.1. Ethical approval and informed consent

Following the publication of SERVE-HF preliminary results in May 2015, we considered ethical to invite our ASV patients to attend the safety procedure developed in our department, with no opinion

expressed by institutional and/or national research committees. Our safety procedure was not a study/protocol but supplementary verification within regular clinical follow-up. Informed consent to attend our safety procedure was obtained from each surviving patient. Regarding deceased patients, the study was retrospective and, as such, formal consent was not sought. No identifying information concerning participants is available in the article.

## 3. Results

### 3.1. Case reports

Deceased patients' clinical characteristics prior to ASV are presented in Table 1. Patient number corresponds to patronymic alphabetical order. All but patient No.7 had a history of cardiovascular disease but only No.8 matched the SERVE-HF patient profile. The four patients with clinical heart failure had had at least one episode of acute cardiac decompensation with emergency hospitalization. The four patients with ischemic cardiopathy had had at least one acute coronary syndrome, with at least one act of coronary artery revascularization in three of them. Regarding cardiac arrhythmia, five patients had permanent atrial fibrillation and there were no cases of paroxysmal supraventricular tachyarrhythmia. Cardiac pacing was cardiac resynchronization therapy-defibrillation related to heart failure in patient No.2. A conventional pacemaker related to bradyarrhythmia had been implanted in patients No.5 and No.6. Nocturnal recording in patient No.6 was related to enrollment in a study on sleep apnea in patients with atrial fibrillation and cardiac pacing. Baseline nocturnal recordings showed that four patients had predominant central sleep apnea and all with > 50% of central respiratory events. No patient had predominant obstructive respiratory events. No patient changed sleep apnea syndrome category upon updating initial nocturnal recording scores according to AASM-2016 guidelines.

ASV characteristics and circumstances of death in the eight deceased patients are presented in Table 2. In patients No.2 and No.5 death occurred 6 and 39 months, respectively, after ASV had been interrupted. In both cases suffocation with the facial mask was the reason for ASV intolerance. In the other six cases ASV was ongoing therapy at the time of death and ran on average for 57 months (range: 15–99) with compliance of 6.9 hours per night (range: 4.2–9.1). In those six patients the apnea-hypopnea index was 43.1 events per hour on average at baseline (range: 35–52.9) and 7.4 events per hour with ASV (range: 2.2–19.2). Patients No.1 and No.4 died 28 and 7 weeks, respectively, after the re-assessment of their case in accordance with our safety procedure and before completion of this procedure in the study population. In these two patients no contra-indications to carrying on ASV had been noted during the re-assessment of their case, in particular as their LVEF was 84% and 76%, respectively. All the patients died while they were hospitalized except patient No.6 who died at home and patient No.7 who committed suicide in his car. In patient No.1 the dominant health problem was cognitive alteration; he died from cardiac arrest in a context of respiratory infection associated with pulmonary embolism and acute kidney failure. Patients No.2 and No.3 were in end-stage heart failure condition and died, respectively, from ventricular fibrillation despite an implanted defibrillator which delivered several electric shocks and from cardiac asystole. Patients No.4 and No.8 suffered from end-stage lung cancer with multiple metastatic localizations and patient No.6 suffered from end-stage prostate cancer with bone metastases. In these three cases of cancer death occurred in a context of very poor general condition, which deteriorated continuously over several weeks. Patient No.5 had acute respiratory infection resulting in severe deterioration of his general condition and eventually in death. No deaths occurred while the patient was using ASV equipment. In patients who died at night, patient No.1 was in respiratory distress, rendering the use of ASV impossible, and patient No.6 was in a state of emaciation, hindering airtight positioning of the facial mask.

**Table 1**  
Deceased patients' clinical characteristics prior to adaptive servo-ventilation.

	Patient No.							
	1	2	3	4	5	6	7	8
Age, y	86	59	77	83	81	75	61	52
Sex	male	male	male	male	male	male	male	male
BMI, kg/m <sup>2</sup>	26.4	40.6	28.3	36.1	34.3	24.9	28.4	29.8
CV risk factors <sup>a</sup> , n	1	4	1	1	2	2	1	2
Heart failure (HF) <sup>b</sup>	no	yes	yes	no	yes	no	no	yes
Cardiopathy	no	ICP	ICP	HCP	ICP	HCP	no	ICP
LVEF, %	70	40	47	78	39	60	65	32
Cardiac arrhythmia	AF	AF	no	AF	AF	AF	no	no
Cardiac pacing	no	yes	no	no	yes	yes	no	no
Stroke	no	yes	no	yes	yes	yes	no	yes
Respiratory disease	no	COPD	no	no	no	no	no	no
Renal failure <sup>c</sup>	no	no	no	yes	no	no	no	no
Recording for	DS	HF	HF	DS	HF	other <sup>d</sup>	DS	DS
AHI, n/h	44.5	62.5	40.4	52.9	55.1	35.0	45.9	39.8
Central, %	91	18	78	13	44	37	58	73
Obstructive, %	2	20	14	11	0	5	37	17
Mixed, %	7	62	8	76	56	58	5	10
ODI, n/h	29.5	53.0	37.3	52.8	53.0	32.0	48.2	33.6
SaO <sub>2</sub> < 90%, min (%)	0 (0)	168 (47)	50 (13)	87 (20)	29 (7)	90 (22)	437 (94)	4 (1)
SaO <sub>2</sub> at baseline, %	95	95	96	95	98	97	95	98

AF = atrial fibrillation (permanent in all cases); AHI = apnea-hypopnea index: mean number of apneas and hypopneas per hour of recording (central, obstructive, mixed AHI: in percentage of global AHI); DS = diurnal somnolence; HCP = hypertrophic cardiopathy; ICP = ischemic cardiopathy; LVEF = left ventricular ejection fraction; ODI = oxygen desaturation index: mean number of oxygen desaturation episodes ≥3% per hour of recording; SaO<sub>2</sub> < 90% = time with arterial oxygen saturation < 90% and percentage of recording time.

<sup>a</sup> Cardiovascular (CV) risk factors: systemic hypertension, dyslipidemia, diabetes, tobacco.

<sup>b</sup> At least one episode of acute cardiac decompensation with hospitalization.

<sup>c</sup> Plasma creatinine > 140 μmol/L.

<sup>d</sup> Study discharge.

### 3.2. Surviving versus deceased ASV patients

Surviving and deceased patients' available clinical characteristics prior to ASV are presented in Table 3. LVEF is not reported as it was lacking in particular in patients who had no cardiovascular disease therefore no indications for cardiac investigation. Among the four surviving patients with stroke, one had permanent and another paroxysmal atrial fibrillation. Of the five deceased patients with stroke, four had permanent atrial fibrillation.

### 3.3. Consequences of our safety procedure

Among the 26 patients who underwent our safety procedure ASV was interrupted in 4 surviving patients due to their LVEF, respectively, 35%, 38%, 33% and 41%. Actually, mixed respiratory events were predominant in three of these patients. Nevertheless, as a precaution, low LVEF was considered as a likely main risk factor for complications relating to ASV, irrespective of the nature of the sleep apnea. Alternative solutions were continuous positive airway pressure (CPAP) ventilation in two cases and nocturnal oxygen therapy in one case. The fourth of these patients was also candidate for cardiac resynchronization therapy and was hyper-responsive to it, which was associated with

**Table 2**  
Adaptive servo-ventilation (ASV) characteristics and death circumstances in deceased patients.

	Patient No.							
	1	2	3	4	5	6	7	8
Reason for ASV	CSAS	MSAS	CSAS	MSAS	MSAS	MSAS	CSAS	CSAS
Device	A	A	A	B	A	A	B	A
Start, mo/yr	08/2014	10/2007	08/2007	09/2010	10/2006	08/2006	10/2009	11/2006
Duration, mo	17	19	78	59	0.25	76	15	99
Compliance, h	7.7	2.5	4.2	7.5	na	8.8	4.3	9.1
Residual AHI, n/h	2.2	na	3.8	19.2	na	7.7	6.4	5.2
Contra-indication <sup>a</sup>	no	no	no	no	no	no	no	yes
Stop before death	no	yes <sup>b</sup>	no	no	yes <sup>b</sup>	no	no	no
Death venue	hospital	hospital	hospital	hospital	hospital	home	car	hospital
Time	night	night	day	day	night	night	day	day
Ventilator on <sup>c</sup>	no	na	no	no	na	no	no	no
Main disease	dementia	HF	HF	cancer	HF	cancer	depression	cancer
Acute situation	sepsis	VF	asystole	end-stage	sepsis	end-stage	suicide	end-stage

A = ResMed Autoset CS 2; AHI = apnea-hypopnea index; B = Respirationics BiPAP autoSV; CSAS = central sleep apnea syndrome; HF = heart failure; MSAS = mixed sleep apnea syndrome; VF = ventricular fibrillation; na = non-available or non-applicable.

<sup>a</sup> According to May 2015 ResMed Safety Notice.

<sup>b</sup> Death 22 months after ASV cessation in patient No. 2 and 38 months in patient No. 5.

<sup>c</sup> Death while ASV was being operating.

**Table 3**

Surviving patients' and deceased patients' clinical characteristics prior to adaptive servo-ventilation (ASV).

	Surviving patients n = 24	Deceased patients n = 8
Age, y	63	72
Male/female, n	21/3	8/0
BMI, kg/m <sup>2</sup>	30.8	31.1
Cardiopathy <sup>a</sup> /Heart failure <sup>b</sup> , n	10/6	6/4
Permanent atrial fibrillation, n	3	5
Cardiac pacing, n	2	3
Stroke, n	4	5
Respiratory disease, n	3	1
Recording for DS/HF/Other <sup>c</sup> , n	15/2/7	4/3/1
AHI, n/h	50.4	47.0
Central/Obstructive/Mixed, %	39/38/23	52/13/35
ODI, n/h	48.5	42.4
SaO <sub>2</sub> < 90%, min (%)	59 (14)	108 (25)
ASV for CSAS/MSAS, n	11/6	4/4
After CPAP failure <sup>d</sup> , n	7	0
Device A/B/Weinmann, n	5/18/1	6/2/0
Duration, mo	39	45
Compliance, h	6.7	6.3
Residual AHI, n/h	4.2	7.4
Contra-indication <sup>e</sup> , n	1	1

See legend in Tables 1 and 2.

<sup>a</sup> Ischemic, hypertrophic, valvular or idiopathic dilated cardiopathy.

<sup>b</sup> At least one episode of acute cardiac decompensation with hospitalization.

<sup>c</sup> In alive patients: snoring (n = 4), fatigue (n = 1), polycythaemia (n = 1), resistant hypertension (n = 1).

<sup>d</sup> Continuous positive airway pressure (CPAP) first with predominant OSAS or MSAS.

<sup>e</sup> According to May 2015 ResMed Safety Notice.

significant alleviation of his apnea load.

#### 4. Discussion

A majority of practitioners managing patients with CHF and sleep apnea expected that the SERVE-HF study would show beneficial effects of ASV on morbidity and mortality in the study population [1,3–8]. Nevertheless, in this study ASV was associated with an increased risk of cardiovascular mortality. It led to recommendations for cessation of ASV to treat predominant central sleep apnea in patients with CHF with significantly reduced LVEF ( $\leq 45\%$ ). Recommendations were also given for alternatives as abstention, CPAP or nocturnal oxygen therapy [4,9–11]. Furthermore, the SERVE-HF study has updated opinion concerning the possible beneficial role of Hunter-Cheyne-Stokes breathing (HCSB) in patients with CHF [12]. This point is highlighted in a post-hoc analysis of the SERVE-HF study that reported more hospitalizations for worsening heart failure in patients with a proportion of HCSB  $\geq 20\%$  at baseline [13]. Lowering HCSB load in patients with CHF then would appear detrimental. In this post-hoc analysis it was also observed that the increased risk of cardiovascular death associated with ASV use concerned patients with LVEF  $\leq 30\%$  in particular. Having occurred prior to admission to hospital, many deaths remained of uncertain cause despite their being considered as cardiovascular deaths and were presumed to be sudden death. It was noted that deaths did not occur specifically during ventilation use and that no evidence appeared regarding the role of the ASV device adjustments such as values of inspiratory and expiratory pressures.

Increased mortality had already been observed in the CANPAP study in patients with CHF with reduced contractility and with predominant central sleep apnea treated with CPAP [3]. It can be remarked that the deaths remained of undetermined causes as in the SERVE-HF study. To the best of our knowledge, apart from the CANPAP and SERVE-HF studies, no cases of death related to the use of a positive

airway pressure device, ASV included, have been reported as being associated with or responsible for death of patients with CHF and treated for central and/or obstructive sleep apnea [5–9,14–16]. Nevertheless, in the studies that showed a better survival rate in patients with CHF and central sleep apnea treated with CPAP or ASV versus untreated patients, we cannot be sure that no deaths were related to ventilation therapy. In those studies, probably due to lower mortality with ventilation therapy compared to standard care, no particular relationship has ever been evoked between the deaths and the use of a ventilation device.

Relatively few patients were equipped with ASV in our cardiovascular department with a sleep unit from 2006 (our first ASV patient) to 2015. The main reason was that we frequently proposed nocturnal oxygen therapy rather than ASV or CPAP therapy due to patient inclusion in our studies with nocturnal oxygen use in patients with CHF and sleep apnea [17]. In our case series, when ASV was being initiated, only patient No.8 matched the main characteristics of the SERVE-HF patients, i.e. with symptomatic CHF, with a  $\leq 45\%$  LVEF and predominant central sleep apnea. Only six patients were still treated with ASV at the time of their death but we obtained information on the exact circumstances of death in each. Of those six patients only one unsurprisingly died from a cardiovascular cause i.e. asystole in an end-stage heart failure condition. The only case of sudden death, with documented ventricular fibrillation, occurred in patient No.2 in whom ASV had been interrupted 22 months previously. Our cohort consisted of heterogeneous patient phenotypes, which is probably the main reason why we observed various causes of death and no predominance of cardiovascular causes as in the SERVE-HF study. Nevertheless, our series comprised seven out of eight patients with cardiovascular disorders, only one of whom had a CHF SERVE-HF-like profile.

#### 5. Conclusion

This series provides information on the causes of death in patients treated with ASV for predominant central or mixed sleep apnea in seven out of eight patients with cardiovascular disorders including one with a CHF SERVE-HF profile. Cardiovascular deaths were not predominant. No relationship became apparent between sleep apnea or ASV and death. Further study will be required to clarify the risks associated with ASV in patients with cardiovascular disease [18].

#### Conflicts of interest

P Bordier and A Lataste have no conflict of interest to disclose.

#### Acknowledgements

Special thanks to Alan Metcalfe for his help in the present article.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2018.11.017>.

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